INTERACTIONS BETWEEN ACTIVIN AND ESTROGEN SIGNALING IN THE OVARY

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INTRODUCTION

The steroid hormone estrogen and the TGF-β superfamily member activin are both produced in the ovary. In addition to their roles in many extragonadal tissues, they both have intra-ovarian functions (1, 2). Emerging evidence has indicated an interaction of these two signaling pathways. Our research focuses on the function of activin in ovarian follicle development and the interactions between activin and estrogen signaling in the ovary.

RESULTS

Based on the fact that estrogen and activin can impact early follicle formation and development, we examined the effects of neonatal exposure to the phytoestrogen genistein, synthetic estrogen diethylstilbestrol (DES), and the natural estrogen estradiol (E2) on the expression of the key factors involved in activin signaling in the mouse ovary. Neonatal exposure to these compounds induced multioocytic follicle formation and decreased activin β-subunit mRNA and protein levels (Fig. 1). Consistent with local loss of β-subunit expression, activin-dependent signaling was decreased as measured by phosphorylated Smad 2. Estrogen also suppressed activin subunit gene promoter activities, suggesting a direct transcriptional effect (3).

In an effort to examine the effects of activin on ovarian gene expression, we performed a microarray study, and identified the estrogen receptor β (ERβ) as an activin up-regulated gene. Further studies showed that both ERα and ERβ mRNA and protein levels were induced by activin A, and this was a direct effect at the level of gene transcription. We also found that the activin signaling mediators Smad 2 and Smad 3 are both involved in regulating ER levels. To investigate the effect of activin *in vivo* and thus its biological significance, we examined ER expression in inhibin transgenic mice that have decreased activin expression and discovered that these mice had decreased ERα and ERβ expression in the ovary, suggesting an important role for activin in maintaining ER levels (Fig. 2) (4).

CONCLUSIONS

Overall, our studies demonstrate that activin subunits are targets of estrogen action in the early mouse ovary, and activin in turn regulates the expression of ERs. These studies thus reveal an important interplay between activin and estrogen signaling. Given the fact that estrogen and TGF-β superfamily members including activin play important roles in many systems and are closely linked to many forms of cancers, the findings from these studies will add significantly to our knowledge on and hence the treatment of human diseases.

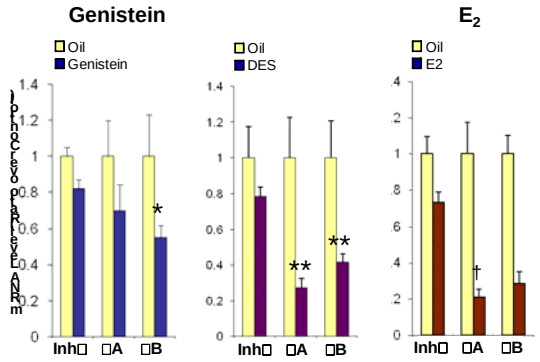

Fig. 1. Neonatal genistein, DES or E2 treatments decreased activin subunit mRNA levels in the mouse ovary.

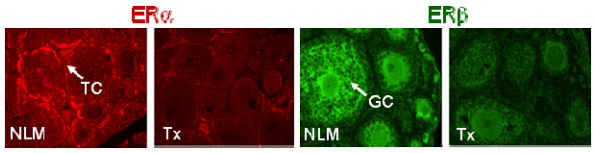

Fig. 2. ERα and ERβ protein levels are decreased in the ovaries from the MT-α inhibin transgenic mice. NLM: normal littermates. Tx: transgenic. TC: theca cells. GC: granulosa cells.

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ACKNOWLEDGMENTS

This work was supported by NIH Endocrinology Training Grant T32 DK007169 and Program Project Grant HD91291.